PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :		(11) International Publication Number:	WO 93/02744
A61N 1/36	A1	(43) International Publication Date:	18 February 1993 (18.02.93)

(21) International Application Number: PCT/US92/06386

(22) International Filing Date: 6 August 1992 (06.08.92)

(30) Priority data:
742,889 9 August 1991 (09.08.91) US

(71) Applicant: CYBERONICS, INC. [US/US]; Suite 1000, 17448 Highway 3, Webster, TX 77598 (US).

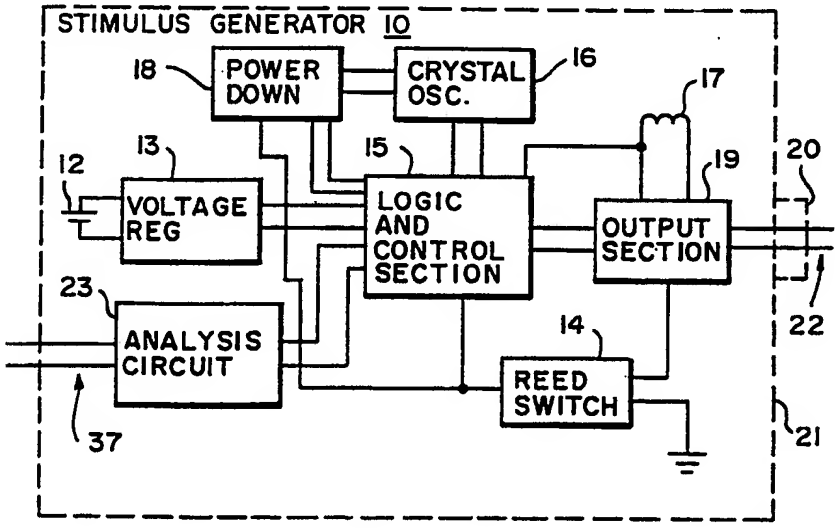
(72) Inventors: TERRY, Reese, S., Jr. ; 15210 Redwood Run Court, Houston, TX 77062 (US). WERNICKE, Joachim, F. ; 2605 Ryder Court, League City, TX 77573 (US).

(74) Agents: GREENE, Donald, R. et al.; Leitner, Greene & Christensen, 1735 Jefferson Davis Highway, Suite 203, Arlington, VA 22202-3400 (US).

(81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).

Published
With international search report.

(54) Title: TREATMENT OF ANXIETY DISORDERS BY NERVE STIMULATION



(57) Abstract

Method and apparatus are disclosed for treating and controlling anxiety disorders by detecting a manifestation of the disorder, and responding to the detection by selectively applying a programmed electrical signal to the patient's vagus nerve for stimulation thereof to increase vagal activity and vagal tone and thereby alleviate the symptoms of the disorder. The electrical signal may be appplied automatically to the vagus nerve in response to detection of a tachycardia, unrelated to exercise, or of hyperventilation, or of excessive perspiration or of collapse of the patient as indicative of onset of the disorder. Alternatively, the electrical signal is selectively applied at will (manually) to the vagus nerve, such as by patient activation of the signal generator (10). Parameter values of the electrical signal including pulse width, output current, frequency, on time and off time, are selectively programmable.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FI	Finland	MN	Mongolia
AU	Australia	FR	France	MR	Mauritania
BB	Barbados	GA	Gabon	MW	Malawi
BE	Belgium	GB	United Kingdom	NL	Netherlands
BF	Burkina Faso	GN	Guinea	NO	Norway
BG	Bulgaria	GR	Greece	NZ	New Zealand
BJ	Benin	HU	Hungary	PL	Poland
BR	Brazil	IE	Ireland	PT	Portugal
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	RU	Russian Federation
CG	Congo	KP	Democratic People's Republic of Korea	SD	Sudan
CH	Switzerland			SE	Sweden
CI	Côte d'Ivoire	KR	Republic of Korea	SK	Slovak Republic
CM	Cameroon	LI	Liechtenstein	SN	Senegal
CS	Czechoslovakia	LK	Sri Lanka	SU	Soviet Union
CZ	Czech Republic	LU	Luxembourg	TD	Chad
DE	Germany	MC	Monaco	TG	Togo
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America

TREATMENT OF ANXIETY DISORDERS BY NERVE STIMULATION

Background of the Invention

The present invention relates generally to methods and apparatus for treating or controlling medical, psychiatric or neurological disorders by application of modulating electrical signals to a selected nerve or nerve bundle of the patient, and more particularly to techniques for treating patients with anxiety disorders by application of such signals to the vagus nerve, using an implantable neurostimulating device. Specifically, the invention is directed toward treating the symptoms of disorders such as anxiety and panic attacks by selective modulation of vagus nerve activity.

Anxiety disorders are among the most common psychiatric illnesses. In their more severe forms, such disorders can leave the patient dysfunctional. In addition to the subjective feelings of anxiety and panic, physiological changes such as tachycardia, palpitations, sweating and trembling are reported. Secondary insomnia is commonly observed in patients with anxiety, with complaints of difficulty in getting to sleep and of frequent waking from sleep. Symptoms of anxiety often accompany withdrawal from sedatives, or may arise from the use of stimulants such as amphetamines. In Arch. Gen. Psych. (1989) 46:153-156, George et al. reported that lactate infusion and hyperventilation produce subjective symptoms and objective signs of anxiety, and are associated with decreased vagal tone (i.e., decreased parasympathetic activity).

A decrease in vagal activity appears to be associated with panic attacks, and may also be associated with excessive anxiety. Accordingly, we postulate that stimulation of the vagus nerve (the tenth cranial nerve) can be beneficially applied to provide effective treatment of such disorders.

The nerves in the human body are composed of thousands of fibers having different sizes designated by groups A, B and C, carrying signals to and from the brain and other

parts of the body. The vagus nerve, for example, may have approximately 100,000 fibers (axons) of the three different types, each of which carries such signals. Each axon of that nerve only conducts in one direction, in normal circumstances. The A and B fibers are myelinated, that is, they have a myelin sheath in the form of a substance largely composed of fat. On the other hand, the C fibers are unmyelinated.

Myelinated fibers are typically larger, have faster electrical conduction and much lower electrical stimulation thresholds than the unmyelinated fibers. Along with the relatively small amounts of electrical energy needed to stimulate the myelinated fibers, it is noteworthy that such fibers exhibit a particular strength-duration curve in response to a specific width and amplitude of stimulation pulse.

The A and B fibers are stimulated with relatively narrow pulse widths, from 50 to 200 microseconds (μs), for example. A fibers exhibit slightly faster electrical conductivities than the B fibers, and slightly lower electrical stimulation thresholds. The C fibers are relatively much smaller, conduct electrical signals very slowly, and have high stimulation thresholds typically requiring wider pulse widths (e.g., 300-1000 μs) and higher amplitudes for activation. Although the A and B fibers may be selectively stimulated without also stimulating the C fibers, the magnitude and width of the pulse required for stimulating the C fibers would also activate A and B fibers.

Although electrical stimulation of the nerve fiber typically activates neural signals in both directions (bidirectionally), selective unidirectional stimulation is achievable through the use of special nerve electrodes and stimulating waveforms. As noted above, each axon of the vagus nerve normally conducts in only one direction.

In a paper on the effects of vagal stimulation on experimentally induced seizures in rats (Epilepsia 1990, 31 (Supp 2): S7-S19), Woodbury has noted that the vagus nerve is

composed of somatic and visceral afferents (i.e., inward conducting nerve fibers which convey impulses toward a nerve center such as the brain or spinal cord) and efferents (i.e., outward conducting nerve fibers which convey impulses to an effector to stimulate it and produce activity). The vast majority of vagal nerve fibers are C fibers, and a majority are visceral afferents having cell bodies lying in masses or ganglia in the neck. The central projections terminate, by and large, in the nucleus of the solitary tract which sends fibers to various regions of the brain (e.g, the hypothalamus, thalamus, and amygdala); others continue to the medial reticular formation of the medulla, the cerebellum, the nucleus cuneatus and other regions.

Woodbury further notes that stimulation of vagal nerve afferent fibers in animals evokes detectable changes of the EEG in all of these regions, and that the nature and extent of these EEG changes depends on the stimulation parameters. Chase, in Exp Neurol (1966) 16:36-49, had also observed that vagal activation can affect the EEG activity of certain parts of the brain. The applicants herein postulate that synchronization of the EEG may be produced when high frequency (> 70 Hz) weak stimuli activate only the myelinated (A and B) nerve fibers, and that desynchronization of the EEG occurs when intensity of the stimulus is increased to a level that activates the unmyelinated (C) nerve fibers. Woodbury also observes that vagal stimulation can produce widespread inhibitory effects on seizures and certain involuntary movements.

Extra-physiologic electrical stimulation of the vagus nerve has previously been proposed for treatment of epilepsy and various forms of involuntary movement disorders. Specifically, in U.S. Patent 4,702,254 issued October 27, 1987 to J. Zabara (referred to herein as "the '254 patent"), a method and implantable device are disclosed for alleviating or preventing epileptic seizures, characterized by abnormal neural discharge patterns of the brain. The '254 patent describes an implantable neurocybernetic prosthesis (NCP)

which utilizes neurocybernetic spectral discrimination by tuning the external current of the NCP generator to the electrochemical properties of a specific group of inhibitory nerves that affect the reticular system of the brain. These nerves are embedded within a bundle of other nerves, and are selectively activated directly or indirectly by the tuning of the NCP to augment states of brain neural discharge to control convulsions or seizures. According to the patent, the spectral discrimination analysis dictates that certain electrical parameters of the NCP pulse generator be selected based on the electrochemical properties of the nerves desired to be activated. The patent further indicates that the optimum sites for application of the NCP generator output to produce the desired effects are the cranial nerves in general, and the vagus nerve in particular.

The NCP disclosed in the '254 patent may be activated either manually or automatically, to provide treatment for the duration of the seizure. Manual activation is performed when the patient experiences the aura at onset of the seizure. Alternatively, automatic activation may be triggered upon detection of instantaneous changes in certain state parameters immediately preceding or at onset of a seizure. Additionally, a prophylactic or preventive mode may be employed in which the NCP is activated periodically to reduce the occurrence and/or the intensity of the seizures. The NCP stimulator of the '254 patent is implanted in the patient's chest and is connected to electrodes installed at the selected point of signal application at the nerve site with the more negative electrode situated closer to the brain and the positive electrode further from the brain, along the vagus nerve.

The present invention has as its principal objective the application of techniques of selective modulation of vagus nerve electrical activity, using a neurostimulator device which may be implantable, or used external to the body with only a small portion of the circuitry implanted or with only the nerve electrode(s) and associated lead(s) implanted

percutaneously in the body, to the treatment of anxiety disorders including excessive anxiety and panic attacks.

Summary of the Invention

Briefly, the present invention is directed to methods and devices for treating and controlling anxiety disorders by selective stimulation of the vagus nerve to increase vagal tone and vagal activity, and, in appropriate cases, to increase synchronization of the patient's EEG. The apparatus of the invention employs a neurostimulator (preferably but not necessarily implantable) to selectively apply the therapy to treat and control excessive anxiety and panic attacks. The therapy is delivered in a manner to modulate the vagal activity of the patient in a predetermined manner to treat and relieve the symptoms of the disorder, although it would not necessarily be expected to be effective in alleviating the underlying root cause of the disorder. The neurostimulator is programmed by the attending physician to generate output pulses having electrical parameters which will provide the desired therapeutic modality when applied to the vagus nerve of the patient for stimulation thereof. At some stimulus parameters, the vagal stimulation will synchronize the EEG, with a resultant beneficial effect on treatment of the disorder where increased beta wave activity is present.

Selection among various strategies for vagal modulation to treat anxiety disorders will depend on a number of factors. These include (i) a consideration of which of the nerve fibers are to be subjected to the modulation; (ii) the modality for achieving synchronization of the EEG; (iii) whether a physiologic signal is generated indicative of onset of the disorder, and if so, the ease with which such a signal may be detected and employed to trigger the modulation; and/or (v) whether a "carryover" or refractory period occurs after modulation in which the benefit of the modulation is maintained. Although these are not all of the factors to be considered for selecting a stimulation strategy for treatment

of a particular disorder, nor necessarily listed in order of importance, they are indicative of considerations which may apply in a specific case.

In the treatment, the invention uses different signal parameters and threshold curves to activate the various fibers of the patient's vagus nerve for selective modulation thereof. By appropriately setting pulse width and amplitude of the electrical signal to be delivered by the neurostimulator to the patient's vagus nerve, the nerve fibers can be selectively stimulated, such as A and not B and C; or A and B, but not C; or A, B and C. Various related factors, however, must be considered in the selection process. For example, because the C fibers conduct signals very slowly, they are not highly responsive to techniques of fast stimulation. They become refractory after a relatively short period of stimulation. Therefore, if the treatment called for increasing synchronous activity of the EEG by stimulation of the C fibers at 90 Hz, it would be prudent to use a short pulse train for the stimulus. The fibers would become refractory to the stimulation within a relatively short time interval and thus incapable of tracking the pattern of a longer train. After a suitable recovery period, another short pulse train may be applied to achieve further treatment. The precise pattern to be used, e.g., the length of the time intervals on and off, will depend upon and be adjusted to the individual patient and the specific nature of the anxiety disorder being treated.

Proper designation of amplitude and frequency range of the applied signals allows tuning of the fibers for EEG synchronization, for further control of the treatment. Synchronization of the EEG is typically achieved by stimulation at frequencies in the range above 75 Hz at signal levels less than 3 volts. The actual voltage required depends on the type and geometry of the electrode and the impedance of the electrode-tissue interface.

According to the invention, the basic stimulation strategy calls for modulating the electrical activity of the

vagus nerve primarily to increase vagal tone and activity by applying a preprogrammed electrical pulse waveform from the stimulus generator to the nerve. As indicated above, for some patients it is desirable to program the waveform in a way to increase EEG synchronization when the signal is applied to the vagus nerve. The preferred detection strategy for automatic application of the stimulus is to use standard cardiac leads and sense circuitry to detect a tachycardia in the absence of physical exercise and/or to use an impedance measuring circuit to detect hyperventilation, each of which is a common manifestation of or associated with abnormal fear, anxiety or panic attacks. Less commonly, the patient may experience fainting in such cases, so that a detector suitable for sensing loss of consciousness by the patient may be useful. Alternatively, the neurostimulator may be activated manually by the patient (or by the attending physician) when such fear, anxiety or panic is sensed. This, of course, would avoid the need for surgically implanting one or more detectors.

Broadly, then, the present invention is directed to apparatus and methods which employ a neurostimulator device, preferably implantable, for treating and controlling anxiety disorders through nerve stimulation. The modulating signals applied to the vagus nerve may stimulate or inhibit other neural signals to produce excitatory or inhibitory neurotransmitter release, but for purposes of this disclosure both situations are included within the term "stimulating". It should be emphasized that although the preferred nerve site for application of the modulating signals is the vagus nerve, effective treatment may be achieved through application of the stimulus to one or more other nerves, particularly among the cranial nerves, and such treatment is deemed to be within the ambit of the present invention.

Accordingly, it is a more specific object of the invention to provide methods and apparatus for treating and controlling anxiety disorders by applying electrical stimuli to the patient's vagus nerve or other cranial nerve, to

activate a specific group of fibers from among all of the fiber groups of the selected nerve(s), and to selectively increase vagal tone and activity and/or synchronize the patient's EEG.

Another object of the invention is to provide methods of treating and controlling anxiety disorders by sensing a symptom or manifestation of the disorder and thereafter automatically or manually effecting modulation of vagal activity through the application of preselected stimuli to the patient's vagus nerve to suppress the disorder.

Brief Description of the Drawings

The above and still further objects, aspects, features and attendant advantages of the present invention will be better understood from a consideration of the ensuing detailed description of a presently preferred embodiment and method thereof, taken in conjunction with the accompanying drawings, in which:

FIG. 1 is a simplified block diagram of an implantable neurostimulator electronics package (stimulus generator) for use (with appropriate parameter settings and ranges) in treating anxiety disorders according to the present invention;

FIG. 2 is a simplified fragmentary illustration of a preferred embodiment of the stimulus generator and lead/electrode systems of the neurostimulator and associated detection devices implanted in the patient's body;

FIG. 3 is a detailed fragmentary illustration of the nerve electrode as implanted on the vagal nerve in the neck of the patient for modulating vagal activity; and

FIG. 4 is an illustrative idealized electrical output signal waveform of the stimulus generator useful for clarifying relevant parameters of the signal developed by the stimulus generator for application to the nerve.

Description of the Presently Preferred Embodiment and Method

Referring now to the drawings, a block diagram of the basic components of the stimulus generator of a neurostimulator and their interrelationship is illustrated in FIG. 1, and further details of location of an implantable version of the device and the associated lead/electrode system are shown in FIGS. 2 and 3. A generally suitable form of neurostimulator for use in the apparatus of the present invention is disclosed in copending U.S. patent application Ser. No. 07/434,985, filed November 10, 1989 in the names of Anthony J. Varrichio et al. (referred to herein as "the '985 application"), assigned to the same assignee as the instant application. The specification of the '985 application is incorporated herein in its entirety by reference, but certain portions of it are summarized in this application for the sake of convenience to the reader.

The neurostimulator utilizes a conventional microprocessor and other standard electrical and electronic components, and in the case of an implanted device, communicates with a programmer and/or monitor located external to the patient's body by asynchronous serial communication for controlling or indicating states of the device. Passwords, handshakes and parity checks are employed for data integrity. The neurostimulator also includes means for conserving energy, which is important in any battery operated device and especially so where the device is implanted for medical treatment of a disorder, and means for providing various safety functions such as preventing accidental reset of the device.

The stimulus generator 10 (FIG. 1) is preferably adapted to be implantable in the patient's body, in a pocket formed by the surgeon just below the skin in the chest as shown in FIG. 2, although a primarily external neurostimulator may alternatively be employed. The neurostimulator also includes implantable stimulating electrodes (described below) together with a lead system 22 for applying the output signal of the stimulus generator to the patient's vagus

nerve. Components external to the patient's body include a programming wand for telemetry of parameter changes to the stimulus generator and monitoring signals from the generator, and a computer and associated software for adjustment of parameters and control of communication between the generator, the programming wand and the computer. The external components of the system are not shown in the drawings.

In conjunction with its microprocessor-based logic and control circuitry, the stimulus generator 10 or other implanted or external circuitry may include detection circuitry for sensing an event indicative of an abnormality to trigger automatic delivery of the stimulating signal. For example, a conventional cardic lead and associated electrodes may be implanted in a chamber in the right side of the patient's heart, or conventional impedance measuring electrodes may be implanted in the patient's chest, or a conventional activity sensor which is modified to detect collapse of the patient, for detecting tachycardia, hyperventilation, or fainting of the patient as a manifestation of the anxiety disorder. Such techniques and devices will be discussed further in conjunction with the description of FIG. 2. Since the use of such detection systems can involve complex and delicate surgical implantation procedures as well as the use of associated sense signal analysis or recognition circuitry, it would be preferable where the patient's condition permits, for the treatment to be administered upon manual activation of the stimulaus generator by the patient in recognition that an attack has begun.

As shown in FIG. 1, stimulus generator 10 includes a battery (or set of batteries) 12, which may be of any reliable long-lasting type conventionally employed for powering implantable medical electronic devices (such as batteries employed in implantable cardiac pacemakers or defibrillators). In the preferred embodiment of the stimulus generator, the battery is a single lithium thionyl chloride cell. The terminals of the cell 12 are connected to the input side of a voltage regulator 13. The regulator smoothes

the battery output to produce a clean, steady output voltage, and provides enhancement thereof such as voltage multiplication or division if necessary for a specific application.

Regulator 13 supplies power to logic and control section 15, which includes a microprocessor and controls the programmable functions of the device. Among these programmable functions are output current, output signal frequency, output signal pulse width, output signal on-time, output signal off-time, daily treatment time for continuous or periodic modulation of vagal activity, and output signal-start delay time. Such programmability allows the output signal to be selectively crafted for application to the stimulating electrode set (FIGS. 2 and 3) to obtain the desired modulation of vagal activity for treatment and control of the disorder. Timing signals for the logic and control functions of the generator are provided by a crystal oscillator 16. A magnetically-actuated reed switch 14 is incorporated in the electronics package to provide the generator with manual activation capability (by use of an external magnet, not shown, placed immediately adjacent to the package or its implant site).

Built-in antenna 17 enables communication between the implanted stimulus generator and the external electronics (including both programming and monitoring devices) to permit the device to receive programming signals for parameter changes, and to transmit telemetry information, from and to the programming wand. Once the system is programmed, it operates continuously at the programmed settings until they are reprogrammed (by the attending physician) by means of the external computer and the programming wand.

A power down circuit 18 is electrically connected to reed switch 14, logic/control circuit 15 and crystal oscillator 16. The power down circuit is timed by the clock pulses from the crystal oscillator to reduce power to the microprocessor of section 15 and/or to the oscillator to a point at which the device is essentially in a sleep state but sufficiently alert to be awakened on command. In the

preferred embodiment, power down circuit 18 initiates the power down mode or sleep state automatically, within only a few hours after the device has been activated to generate its programmed stimulating output signal. It is anticipated that a 5 to 10 hour period will be sufficient time in which to control most anxiety or panic attacks, but the period may be longer or shorter depending on the needs of the particular patient. Thereafter, the device remains in the reduced power state until the power down circuit is disabled to wake the microprocessor and/or oscillator by either manual activation of the device (for example, application of a magnet in the immediate vicinity of the reed switch) or by automatic activation upon sensing of a physiological symptom indicative of the onset of an attack. Power down circuits fabricated in CMOS semiconductor circuitry are well known in the integrated circuit field, and such a circuit is readily implemented in the neurostimulator device by persons of ordinary skill in the art.

The reduced power requirement of the device in the interval between episodes of an anxiety disorder assures the availability of sufficient battery power to enable treatment over a much longer period than would otherwise be the case. The result is a significantly increased device lifetime, a substantially increased interval between surgical replacements of the device, and a considerable reduction in device size compared to a device without the power down feature.

Logic and control section 15 of the stimulus generator 10 controls an output section 19 which generates the programmed signal levels to treat the disorder. The output section and its programmed output signal are coupled (directly, capacitively, or inductively) to an electrical connector 20 on the housing 21 of the generator and to lead assembly 22 connected to the stimulating electrodes (FIGS. 2 and 3). If a cardiac lead, impedance electrodes, or collapse detector is to be implanted in the patient for automatically triggering delivery of therapy, a sense signal analysis circuit 23 is provided within the generator housing 21, with

connections to the microprocessor in logic and control section 15 and to the sensing electrodes.

Housing 21 in which stimulus generator 10 is encased is hermetically sealed and composed of a material such as titanium which is biologically compatible with the fluids and tissue of the patient's body. Further details of suitable structure and operation of the neurostimulator, beyond those by which the device is adapted to treat an anxiety disorder, will be found in the '985 application, to which the reader is referred.

FIG. 2 illustrates the preferred location of implanted generator 10, in case 21 with connector 20, in the patient's chest in a cavity formed by the implanting surgeon just below the skin, much as a pacemaker pulse generator would be implanted. A stimulating nerve electrode set 25 (FIG. 3) is conductively connected to the distal end of insulated electrically conductive lead assembly 22 which is attached at its proximal end to connector 20. Electrode set 25 is a bipolar stimulating electrode, preferably of the type described in U.S. Patent 4,573,481 issued March 4, 1986 to Bullara. The electrode assembly is surgically implanted on the vagus nerve 27 in the patient's neck. The two electrodes 25-1 and 25-2 are wrapped about the vagus nerve, and the assembly is secured to the nerve by a spiral anchoring tether 28 preferably as disclosed in U.S. Patent 4,979,511 issued December 25, 1990 to Reese S. Terry, Jr. and assigned to the same assignee as the instant application. Lead(s) 22 is secured, while retaining the ability to flex with movement of the chest and neck, by a suture connection 30 to nearby tissue.

The open helical design of electrode assembly 25 (described in detail in the above-cited Bullara patent), which is self-sizing and flexible, minimizes mechanical trauma to the nerve and allows body fluid interchange with the nerve. The electrode assembly conforms to the shape of the nerve, providing a low stimulation threshold by allowing a larger stimulation contact area. Structurally, the

electrode assembly comprises two ribbons of platinum constituting the electrodes which are individually bonded to the inside surface of each of the first two spiral loops 25-1 and 25-2 of a three-loop helical assembly, and the two lead wires are respectively welded to the conductive ribbon electrodes. The remainder of each loop is composed of silicone rubber, and the third loop acts as the tether 28 for the electrode assembly. The inner diameter of the helical bipolar electrode assembly may typically be approximately two millimeters (mm), and an individual spiral is about seven mm long (measured along the axis of the nerve).

A conventional cardiac bipolar lead/electrode set 33 may be implanted in the atrium or ventricle in the right side of the patient's heart and connected via leads 37 to a sensing circuit in signal analysis circuit 23 to detect a tachycardia manifested by excessive anxiety, fear or panic (i.e., not a sinus tachycardia). Suitable apparatus and circuitry of this type are entirely conventional in the cardiac pacemaker art. Alternatively, a conventional device 42 for measuring electrical impedance variations with changes in the patient's respiration rate may be implanted in the form of electrodes and associated circuitry into the patient's chest, to detect hyperventilation attributable to anxiety or panic. In this case, the impedance measuring device is electrically connected to leads 37 and an appropriate signal analysis circuit 23 of stimulus generator 10 to trigger the delivery of the programmed output pulses from the generator when the detected impedance exceeds a predetermined threshold.

Still another form of detection device which may be suitable in some instances to trigger application of the pulse waveform to the vagus nerve is a motion detector 45 implemented to sense sudden movement indicative of patient collapse, whether in a faint or because of sudden weakness. For example, the signal analysis circuit 23 (or an RF detector) may readily be adapted to recognize an abrupt high level signal such as a spike, to cause activation of the

neurostimulator. Yet another alternative is to use an external moisture detector secured to the patient's chest directly against the skin, to detect excessive sweating associated with anxiety or panic attacks.

If the particular patient being treated is not rendered completely dysfunctional by the anxiety disorder, however, it is desirable and preferred that the neurostimulator be arranged for manual activation by the patient instead of or in addition to relying on automatic activation through a device implanted in or worn by the patient. Typically, the patient readily recognizes the symptoms and manifestations of the anxiety disorder, and can act to activate the stimulator at onset of the attack, for example by placing the magnet in position directly over the implanted device to actuate the reed switch. In either event, the stimulus signal is applied continuously (which may include a period during which the signal is alternately on and off) to the vagus nerve for modulation of the vagal activity.

The stimulus generator may be programmed with an IBM-compatible personal computer (not shown) using programming software of the type copyrighted by the assignee of the instant application with the Register of Copyrights, Library of Congress, or other suitable software based on the description herein, and a programming wand (not shown). The wand and software permit noninvasive communication with the generator after the latter is implanted. The wand is preferably powered by internal batteries, and provided with a "power on" light to indicate sufficient power for communication. Another indicator light is preferably provided to show that data transmission is occurring between the wand and the generator.

Operation of stimulus generator 10 to control and treat anxiety disorders will be described with reference to FIG. 4, an idealized representation of the output signal waveform delivered by output section 19 to electrode array 25. This illustration is presented principally for the sake of clarifying terminology, including the parameters of output

signal on-time, output signal off-time, output signal frequency, output signal pulse width, and output signal current.

The preferred range of stimulation parameters for treatment of anxiety disorders and the typical value of each parameter of the stimulating output signal are set forth in the following table.

TABLE I

	Range	Typical
Pulse Width	0.05 - 1.5 millisec (ms)	0.1 ms
Output Current	0.1 - 5.0 milliamp (mA)	1.0 mA
Frequency	5 - 150 Hertz (Hz)	90 Hz
On Time	5 - 5000 sec	10 sec
Off Time	5 - 5000 sec	10 sec
Frequency sweep	40 - 100 Hz	Optional
Random frequency	40 - 100 Hz	Optional

The nature of anxiety disorders does not readily admit of treatment by programming activation according to the circadian rhyhm of the patient or other periodic manner.

Various features may be incorporated into the neurostimulator for purposes of the safety and comfort of the patient. For example, comfort would be enhanced by programming the output stimulus to ramp up during the first two seconds of stimulation, rather than to be delivered abruptly. Also, the implanted generator may be provided with a clamping circuit to limit the maximum voltage, to 14 volts for example, which is delivered to the vagus nerve. Such a maximum limit is designed to prevent damage to the patient's vagus nerve.

The programmable functions and capabilities of the neurostimulator are designed and implemented to permit noninvasive communication with the stimulus generator after it is implanted, which is useful for both activation and monitoring functions. Beyond the essential functions of the device, the programming software may readily be structured to provide straightforward menu-driven operation, HELP func-

tions, prompts, and messages to facilitate simple and rapid programming while keeping the user fully informed of everything occurring at each step of a sequence. Programming capabilities should include capability to modify the adjustable parameters of the stimulus generator and its output signal, to test device diagnostics, and to store and retrieve telemetered data. It is desirable that when the implanted unit is interrogated, the present state of the adjustable parameters is displayed on the monitor of external PC so that the programmer may then conveniently change any or all of those parameters at the same time; and, if a particular parameter is selected for change, all permissible values for that parameter are displayed so that the programmer may select an appropriate desired value for entry into the neurostimulator.

Diagnostics testing should be implemented to verify proper operation of the device, and to indicate the existence of problems such as with communication, the battery, or the lead/electrode impedance. A low battery reading, for example, would be indicative of imminent end of life of the battery and need for implantation of a new device. The nerve electrodes are capable of indefinite use absent indication of a problem with them observed on the diagnostics testing.

Although a preferred embodiment of apparatus and certain preferred methods for treating and controlling anxiety disorders through vagal modulation according to the invention have been described herein, it will be apparent to those skilled in the field from a consideration of the foregoing description that variations and modifications of such embodiments, methods and techniques may be made without departing from the true spirit and scope of the invention. For example, although a totally implantable device is preferred, the electronic energization package may, if desired, be primarily external to the body. Stimulation can be achieved with an RF power device implemented to provide the necessary energy level. The implanted components may be limited to the lead/electrode assembly, a coil and a DC

rectifier. Pulses programmed with the desired parameters would be transmitted through the skin with an RF carrier, and the signal thereafter rectified to regenerate a pulsed signal for application as the stimulus to the vagus nerve to modulate vagal activity. This would virtually eliminate the need for battery changes. The disadvantages of such an implementation are that the external transmitter must be carried by the patient, greater power is required for activation, and the output current to the nerve is less stable.

An external stimulus generator may be employed with leads extending percutaneously to the implanted nerve electrode set. The major problem encountered with this technique is the potential for infection, but it is useful to allow short term testing of the patient to determine whether the disorder is amenable to successful treatment in the particular patient. If it is, a more permanent implant may be provided.

Accordingly, it is intended that the invention shall be limited only to the extent required by the appended claims and the rules and principles of applicable law.

What is claimed is:

1. A method of treating patients with anxiety disorders, which includes detecting a manifestation of the disorder, and, in response, selectively applying a predetermined electrical signal to the patient's vagus nerve for stimulation thereof to alleviate the symptoms of the disorder being treated.

2. The method of claim 1, wherein the predetermined electrical signal is a pulse waveform with signal parameters programmed to increase vagal activity of the patient.

3. The method of claim 2, wherein detecting a manifestation of the disorder is performed for automatic application of the predetermined electrical signal upon such detection.

4. The method of claim 3, wherein the detection is performed by sensing rapid heart rate of the patient not constituting a sinus tachycardia.

5. The method of claim 3, wherein the detection is performed by sensing hyperventilation of the patient.

6. The method of claim 3, wherein the detection is performed by sensing excessive perspiration by the patient.

7. The method of claim 3, wherein the detection is performed by sensing collapse of the patient.

8. The method of claim 2, wherein

the detection is performed by patient recognition of the manifestation, and the signal is manually activated for application to the vagus nerve.

9. The method of claim 1, wherein

the signal is programmed and applied to the vagus nerve to increase the synchronization of the patient's EEG.

10. The method of claim 1, wherein

the parameter values of the electrical signal including pulse width, output current, frequency, on time and off time, are selectively programmable.

11. A neurostimulator for treatment of an anxiety disorder of a patient, comprising:

neurostimulator generator means for generating an electrical output signal,

implantable lead/electrode means adapted to be electrically connected to said neurostimulator generator means for delivering said electrical signal to the vagus nerve of the patient, and

selection means providing selectable parameter values of the electrical signal of the neurostimulator generator means for selectively stimulating the vague nerve to increase the electrical activity thereof and thereby alleviate the disorder.

12. The invention of claim 11, wherein

said electrical signal is a pulse waveform, and

the selection means includes programmable means for programming the signal parameters of the pulse waveform.

13. The invention of claim 12, wherein

the programmable signal parameters of the pulse waveform include pulse width, output current, frequency, on time and off time.

14. The invention of claim 11, further including sensing means for detecting a manifestation of the anxiety disorder.

15. The invention of claim 14, wherein the neurostimulator generator means includes control means for applying the electrical signal to the patient's vagus nerve in response to detection of the manifestation by the sensing means.

16. The invention of claim 15, wherein the sensing means comprises means for detecting a tachycardia in the absence of physical exercise of the patient.

17. The invention of claim 15, wherein the sensing means comprises means for detecting hyperventilation of the patient.

18. The invention of claim 15, wherein the sensing means comprises means for detecting collapse of the patient.

19. The invention of claim 11, further including means for manually activating the neurostimulator generator means to apply the electrical output signal thereof to the patient's vagus nerve.

20. An implantable nerve stimulator for treating patients with anxiety disorders, comprising:

stimulator means responsive when activated for generating a programmable electrical output signal,

implantable lead/electrode means for electrical connection to the stimulator means and to the vagus nerve of the patient for delivering the programmed electrical signal to the vagus nerve, and

sensing means for detecting the onset of an anxiety disorder to be treated, to activate the stimulator means.

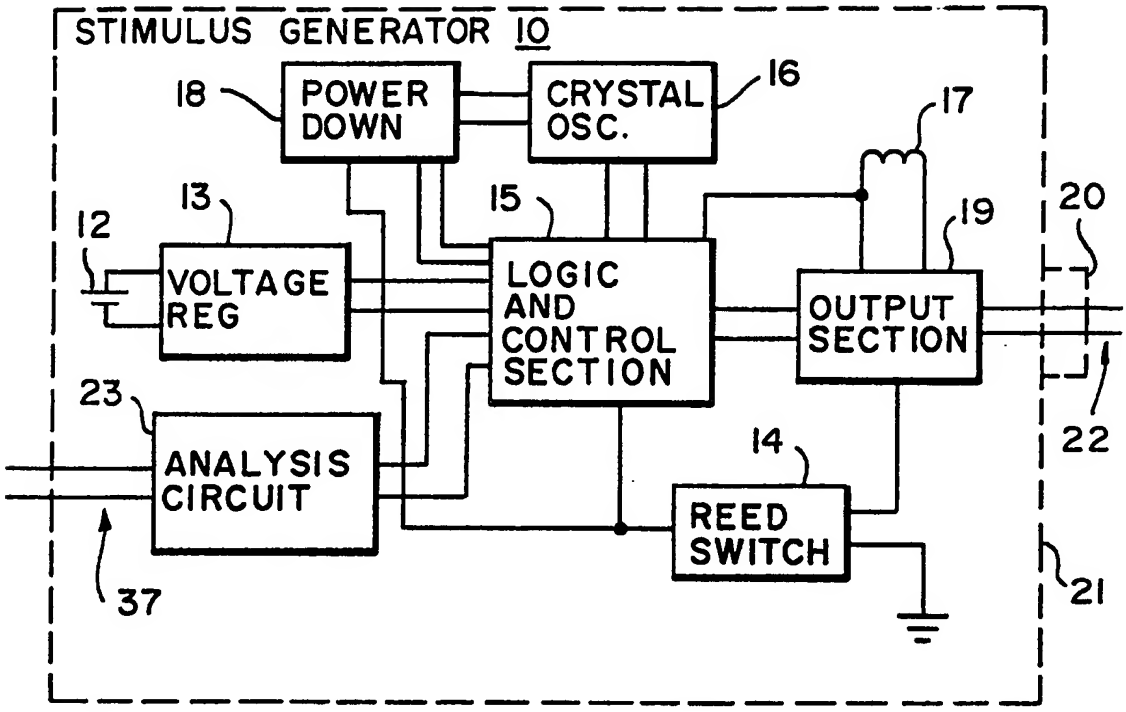


FIG. 1

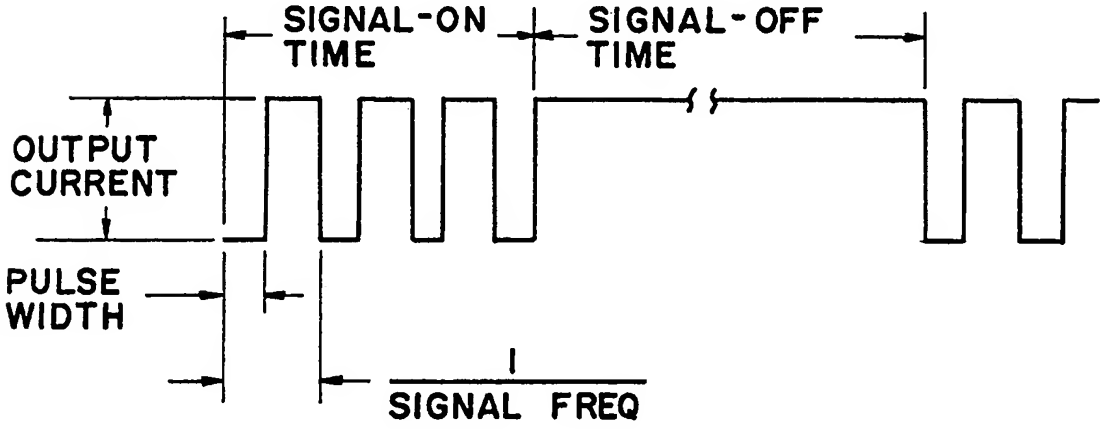


FIG. 4

FIG. 2

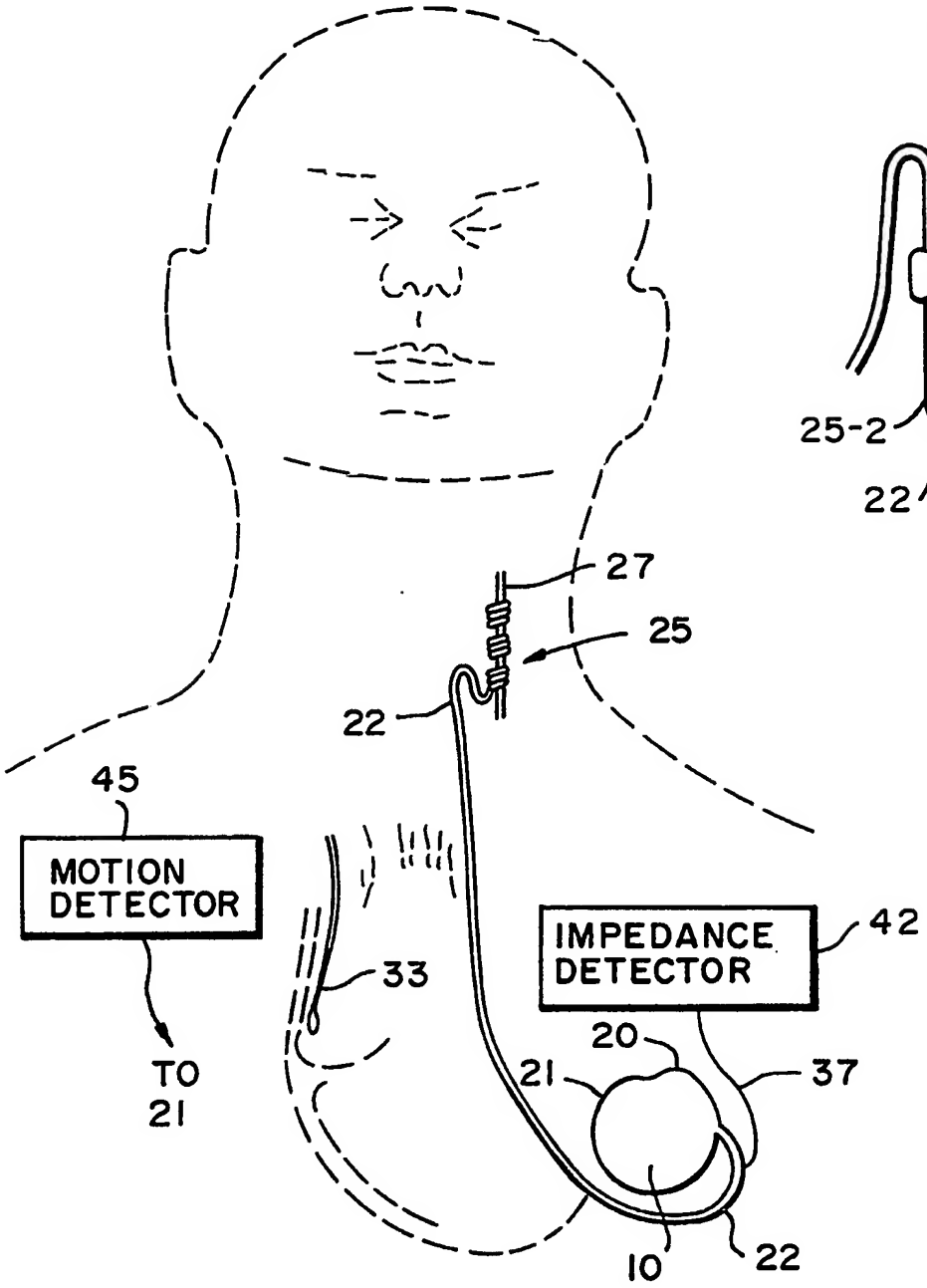
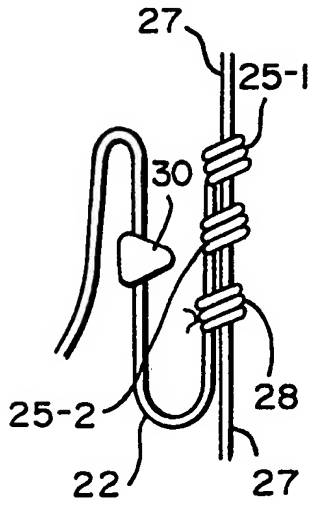


FIG. 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/06386

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61N 1/36
US CL :128/421

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/419.00R, 419.00C, 600/26

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A, 4,865,048 (Eckerson) 12 September 1989 See entire document.	1,2,8,11, 12,19 9
X Y	US,A, 4,867,164 (Zabara) 19 September 1989 See entire document.	1-3,8,10-15 19 and 20 4-7 & 16-18
Y	US,A, 4,503,863 (Katims) 12 March 1985 See col. 6, line 67-col. 7, line 7.	9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 28 SEPTEMBER 1992	Date of mailing of the international search report 17 NOV 1992
Name and mailing address of the ISA/ Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer KENNEDY J. SCHAETZLE Telephone No. (703) 308-2211

Form PCT/ISA/210 (second sheet)(July 1992)*